Regulations Relating to

APPROVAL PROCEDURES FOR CANINE RABIES VACCINES

Excerpts from the

California Code of Regulations

DEPARTMENT OF HEALTH SERVICES
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INFECTIOUS DISEASES BRANCH
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2650. Canine Rabies Vaccine Advisory Committee.

The Director shall appoint a Canine Rabies Vaccine Advisory Committee consisting of 6 to 8 members. The Committee's responsibility shall be to assist the Department in evaluating the effectiveness of canine rabies vaccines. Membership shall include individuals with recognized professional expertise in at least one of the fields of immunology, virology, epidemiology, public health and veterinary medicine. Committee members shall serve without compensation but shall be reimbursed for actual and necessary expenses incurred during service on the committee. Canine rabies vaccines that have been approved by the Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture, shall be evaluated for the degree of effectiveness by the Canine Rabies Vaccine Advisory Committee. In order to evaluate vaccine effectiveness the committee shall:

(a) Review test data submitted by canine rabies vaccine manufacturing firms, for approval of canine rabies vaccines.

(b) Make recommendations for Departmental approval or disapproval of canine rabies vaccines.

(c) Make recommendations concerning approval of any variances from the established standards for acceptance of canine rabies vaccines.

NOTE:
Authority cited: Section 121690(b), Health and Safety Code. Reference: Section 121690(b), Health and Safety Code.

HISTORY

1. New section filed 09-07-90; operative 10-07-90 (Register 90, No. 44).

2651. Approval of Canine Rabies Vaccines.

(a) In order for a canine rabies vaccine to be approved for use in California, it shall adhere to the following requirements:

(1) Meet Animal and Plant Health Inspection Service (APHIS) standards for sterility and safety. Evidence of product conformance to APHIS Standards will be demonstrated by the United States Department of Agriculture (USDA) product licensing; and

(2) If an inactivated vaccine, it shall have a minimal relative potency (RP) at vaccination of at least 2.0 as determined by the National Institute of Health (NIH) Test for potency or if a modified live virus (MLV) vaccine it shall meet USDA potency Requirements; and

(3) Demonstrate an immunity duration of three or more years based on an immunity duration challenge study conducted in conformity with section 2652; and

(4) Comply with the origin and integrity of Rabies Vaccine Virus Requirements in section 2653.

NOTE:
Authority cited: Section 121690(b), Health and Safety Code. Reference: Section 121690(b), Health and Safety Code.

HISTORY

1. New section filed 09-07-90; operative 10-07-90 (Register 90, No. 44).

2652. Immunity Duration-Challenge Studies.

(a) The demonstration of an acceptable immunity duration of three or more years, as shown by adequate challenge studies in dogs, shall be required. However, the above challenge study shall not suffice for acceptance of a subsequent multiple vaccine product that contains the same rabies vaccine as one of two or more component vaccines.

(b) Vaccine Trial Protocols. Vaccine trial protocols shall be submitted to the Department by vaccine manufacturers prior to beginning the immunity duration challenge study. The protocol shall include animals, materials, methods and procedures. The protocol shall include the identification number of each animal, its source and/or that of its mother, if applicable, sex, age, breed and the name, address, and telephone number of a contact person who can verify personal knowledge of the dog's vaccination history. Annual progress reports and a final report of the immunity-duration challenge study shall be submitted to the Department. The reports shall include by date for each dog its rabies antibody titers, other immunizations, medications, illnesses, unusual events and death, if applicable, as well as any changes or developments in reference to animals, materials, methods, and procedures. The Department shall supply firms with an outline to report the foregoing information. The outline will include the following items:

(1) "Protocol for Proposed Rabies Vaccine Immunity Duration Challenge Study";

(2) "Procedures and Preliminary Data Attending Initiation of Canine Rabies Vaccine Immunity Duration Challenge Study";

(3) "Progress Report: One Year Postvaccination";

(4) "Progress Report: Two Years Postvaccination";

(5) "Final Report";

(6) "Results of Challenge"; and

(7) "Progress Report for Three Years Postvaccination."

The Veterinary Public Health Unit, 714 P Street, Room 760, Sacramento, California 95814 will provide this outline upon request.

(c) Dogs Used in Studies. No pound dogs or other dogs of undeterminable rabies vaccination history shall be used in the study. Dogs shall be obtained from the original owner since birth or have verifiable histories. Groups of vaccinates and control dogs shall be of approximately equal composition, according to numbers, sex ratio (approximately 50:50), age, and origin. As much as is possible, dogs of uniform size or conformation shall be used. No dog shall be used which has had prior rabies immunization or which has detectable serum rabies neutralizing antibodies. Dogs under 8 months of age used in studies shall not originate from rabies-immunized mothers. No dog shall be over 1½ years of age at vaccination or when set aside as a control.

(d) Size of Challenge Groups. Challenge groups, both vaccinates and nonimmunized controls, shall each consist of 30 or more dogs at challenge. Any additional (extra or back-up) dogs, intended to replace vaccinates or controls that die prior to challenge, shall be included in either the vaccinate or the control group prior to the initiation of the study and subsequently treated, sampled and reported on as either a vaccinate dog or as a control dog. The use of additional sets of vaccinate and/or control dogs to be challenged simultaneously, or at an earlier or later date, shall not be recognized as representative of separate trials. Instead, the serological results subsequent to vaccination and the reactions to challenge of all groups, sets, and individual dogs

shall be included in the overall analysis on a cumulative basis. Failed antibody response or failed reaction to challenge at any time shall disqualify subsequent trial phases.

(e) Route and Site of Vaccination. MLV vaccines shall be inoculated intramuscularly at one site in the thigh. Inactivated vaccines may be inoculated by any single route and single site which provides the required protection against challenge at least 3 years post vaccination and is shown to be safe. The exact site and route of inoculation shall be described.

(f) New Route and/or Site of Vaccination. If a firm changes its recommended route and/or site of vaccination of a previously approved vaccine, the vaccine shall be tested as a new product, and the firm shall complete another satisfactory immunity duration-challenge study of 3 years or greater duration before the new route and/or site of vaccination shall be approved.

(g) Additional Vaccinations. Excepting food and water, no vaccinate or control dog shall be exposed to any vaccine, drug, or other substance by any route within three weeks prior to any bleeding for antibody test or within three weeks prior to or at any time after challenge with rabies virus except at euthanasia.

(h) Serology. Standard serum virus-neutralization tests done in mice (MSNT) or the rapid rabies fluorescent focus inhibition test (RFFIT) shall be used in comparing the immunogenicity of different products. No substitute test reagents or substitute tests shall be accepted.

(1) Test results shall be reported for the vaccinate group and controls. Serum virus-neutralization titrations shall be performed on sera of (1) all dogs prior to vaccination; (2) vaccinates at the end of post vaccination months 1, 3, 6, 9, 12, 18, 24, 30 and 36 just prior to challenge; (3) controls at the end of month 36 just prior to challenge; and (4) survivors just prior to euthanasia.

(2) At years post vaccination, all vaccinate dogs shall have demonstrable serum rabies antibody titers, the median titer being equal to, or greater than, 1:15 by the MSNT or an equivalent test.

(3) At 3 years post vaccination, at least 90 per cent of vaccinates shall have demonstrable titers by the MSNT, the median titer being equal to, or greater than, 1:10 by the MSNT or an equivalent test.

(i) Incidental Deaths or Deletions. There shall be a complete accounting for all dogs used in the study, including any that die or are killed after the start of the study or any withdrawn from participation for any reason. Each such dog shall be accounted for by dates and details of illness, treatment and death, the cause of death with supportive diagnostic test results, and rabies serology records. Each such dog shall be tested for rabies infection by Fluorescent Rabies Antibody (FRA) test followed by the mouse inoculation test if the FRA test is negative.

j) Challenge Virus and Dose. The challenge virus inoculum, shall be infective carnivore salivary gland suspension supernate of a North American carnivore "street" rabies virus. The dose of challenge virus given shall be estimated by titration prior to challenge and confirmed by titration of residual challenge inoculum. The dose of challenge virus shall be as low as possible while still achieving a mortality of 80 - 100 per cent in controls. The dose given each dog shall not exceed 200,000 mouse intracranial 50 percent lethal doses (MICLD50), or a demonstrably equivalent dose as determined by an alternate method of titration.

(k) Challenge Route and Procedure. Only challenge virus inoculum shall be inoculated into the masseter muscles of vaccinate dogs or control dogs at any time. Challenge virus shall be inoculated intramuscularly into the masseter muscles, the viral dose being divided into two equal parts for bilateral inoculation. Should a challenge route or site other than the intramasseter route be used, the firm employing the route or site shall demonstrate in a trial previously approved by

the Department, the effectiveness and appropriateness of the post challenge holding period and compensate for any related increase in incubation period and decrease in susceptibility. All animals, vaccinates and controls, shall be challenged at the same time, either on an alternate basis (i.e., a vaccinate, followed by a control, followed by a vaccinate, etc.) or the vaccinates shall be challenged first and the controls challenged immediately afterwards. A separate needle and a separate syringe shall be used for each dog.

(l) Individual Enclosure for Each Challenged Dog. Each dog shall be kept in an individual enclosure, preventing its contact with any other animal.

(m) Post challenge Observation Period. Challenged dogs, retained in isolation, shall be observed for a minimum of 90 days prior to final bleeding, euthanasia, and rabies testing of their brains.

(n) Mortality in Challenged Animals. With rare exceptions, all vaccinates shall survive challenge. Eighty to one hundred percent of challenged controls shall die of rabies.

(o) Confirmatory Rabies Diagnostic Tests on Brains of Dogs that Die and on Brains of Survivors. Brains of dogs that die and brains of dogs that survive challenge shall be tested by fluorescent rabies antibody (FRA) test, followed by mouse-inoculation test if the former is negative; dead mice shall be confirmed as rabies-infected by FRA test on their brains. Dogs that die at any time following administration of a live virus vaccine shall be tested for possible rabies vaccine virus infection, using tests suitable to disclose, recover, and identify the strain of vaccine virus.

NOTE:
Authority cited: Section 121690(b), Health and Safety Code. Reference: Section 121690(b), Health and Safety Code.

HISTORY

1. New section filed 09--7-90; operative 10-07-90 (Register 90, No. 44).

2653. Origin and Integrity of Rabies Vaccine Virus.

The Department shall be provided with comprehensive information on the origin, passage level, and sub-passage history of rabies viruses used in the development and production of rabies vaccines being submitted for approval. The integrity of the rabies virus used in the production of the vaccine shall be maintained without further modification once the vaccine is approved for use in the Department's rabies control program.

NOTE:
Authority cited: Section 121690(b), Health and Safety Code. Reference: Section 121690(b), Health and Safety Code.

HISTORY

1. New section filed 09-07-90; operative 10-07-90 (Register 90, No. 44).